

REMARKS

Applicants enclose herewith the Sequence Listing for the above-captioned application and a 3.5" floppy disk containing the Sequence Listing.

The specification has been amended to provide SEQ ID NOS for the sequences disclosed therein. This submission contains no new matter.

A "marked-up" version of the amendments to the specification is attached to this Amendment as required by 37 C.F.R. 1.121.

In accordance with 37 CFR § 1.821(f), I hereby state that the content of the paper and computer readable copies of the Sequence Listing submitted herewith are the same.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Please charge any deficiencies or overpayment to Deposit Account No. 14-1447.

Respectfully submitted,

Date: October 26, 2001

Richard W. Bork
Richard W. Bork, Reg. No. 36,459
Novo Nordisk of North America, Inc.
405 Lexington Avenue, Suite 6400
New York, NY 10174-6401
(212) 867-0123



23650

PATENT TRADEMARK OFFICE

"Marked-Up" Version of Amendments to the Specification

Please replace the paragraph at page 5, line 36 to page 6, line 3 with the following:

--A preferred derivative of somatostatin is:

Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser-Cys-Lys[N^c-γ-Glu(N^a-tetradecanoyl)-OH]-OH (SEQ ID NO: 1) (the two Cys residues are connected via a disulphide bridge).--

Please replace the paragraph at page 6, lines 5-8 with the following:

--A preferred derivative of GLP-1 is:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys[N^c-γ-Glu(N^a-tetradecanoyl)-OH]-OH (SEQ ID NO: 2).--

Please replace the paragraph at page 6, lines 11-14 with the following:

--A preferred ANP analogue is:

Ser-Leu-Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr-Lys[N^c-γ-Glu(N^a-tetradecanoyl)-OH]-OH (SEQ ID NO: 3).--

Please replace the paragraph at page 6, lines 16-18 with the following:

--A preferred type of derivative of a dynorphin analogue is:

Tyr-Gly-Gly-Phe-Cys-Arg-Arg-D-Ala-Arg-Pro-Cys-NH-(CH₂)_n-COOH (SEQ ID NO: 4), wherein n is an integer from 8 to 24.--

Please replace the paragraph at page 6, lines 20-21 with the following:

--A preferred derivative of enterogastrin is:

H-Ala-Pro-Gly-Pro-Arg-Lys(N^c-tetradecanoyl)-OH (SEQ ID NO: 5).--

Please replace the paragraph at page 9, lines 23-24 with the following:

-EXAMPLE 1

Synthesis of For-Nle-Leu-Phe-Nle-Tyr-Lys(N^c-tetradecanoyl)-OH (SEQ ID NO: 6).--

Please replace the paragraph at page 9, line 26 to page 10, line 5 with the following:

--For-Nle-Leu-Phe-Nle-Tyr-Lys-OH (SEQ ID NO: 6), was purchased from Bachem Feinchemikalien AG, Switzerland. The peptide is a potent chemoattractant for human neutrophils. The title compound was prepared by dissolving 17 mg of For-Nle-Leu-Phe-Nle-Tyr-Lys-OH (SEQ ID NO: 6) in 5 ml of DMF and then adding 35 µl l of triethylamine followed by 20 mg of solid tetradecanoic acid succinimidyl-N-hydroxy ester to the solution. The reaction was monitored by RP-HPLC employing a column packed with reversed phase C18 silica material. For the elution was used a gradient from 30% ethanol to 80 % ethanol in 0.1% aqueous TFA. The product was purified on a column (length 250 mm diameter 20 mm) packed with C18 silica reversed phase material. The compound was dissolved in 74% ethanol/0.1% aqueous TFA and subsequently applied to the column and purified at 40 °C by isocratic elution in the same buffer at a flow rate of 6 ml/hour. The yield was 20 mg. The identity of the compound was confirmed by PDMS.--

Please replace the paragraph at page 10, lines 12-16 with the following:

-Reference

The reference compound, For-Nle-Leu-Phe-Nle-Tyr-Lys-OH (SEQ ID NO: 6), was purchased from Bachem Feinchemikalien AG, Switzerland, and used as received. The lipophilicity of the reference compound relative to human insulin was found to be 2.3.--

Please replace the paragraph at page 10, lines 19-20 with the following:

-EXAMPLE 2

Synthesis of H-Tyr-D-Ala-Gly-Phe-Leu-Lys(N^c-tetradecanoyl)-OH (SEQ ID NO: 7).--

Please replace the paragraph at page 10, lines 23-31 with the following:

--The enkephalin derivative H-Tyr-D-Ala-Gly-Phe-Leu-Lys(N^c-tetradecanoyl)-OH (SEQ ID NO: 7) was made from Boc-Tyr-D-Ala-Gly-Phe-Leu-Lys-OH (SEQ ID NO: 7) (A-2435 Bachem Feinchemikalien AG, Switzerland). The Boc-Tyr-D-Ala-Gly-Phe-Leu-Lys-OH (SEQ ID

NO: 7) was acylated using tetradecanoic acid succinimidyl-N-hydroxy ester as described in Example 1. The reaction mixture was evaporated to dryness and the residue was dissolved in TFA and evaporated to dryness, solubilized in ethanol/water/0.1% and purified by RP-HPLC as described in Example 1. The yield was 15 mg.--

Please replace the paragraph at page 11, lines 1-7 with the following:

-Reference

The reference compound, H-Tyr-D-Ala-Gly-Phe-Leu-Lys-OH (SEQ ID NO: 7), was synthesized from Boc-Tyr-D-Ala-Gly-Phe-Leu-Lys-OH (SEQ ID NO: 7) by dissolving 20 mg of this compound in 200 µl of TFA and evaporating to dryness. The residue was dissolved in 5% acetic acid and freeze dried. The lipophilicity of the reference compound relative to human insulin was found to be 3.0×10^3 .--

Please replace the paragraph at page 11, lines 10-12 with the following:

-EXAMPLE 3

Synthesis of H-Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr-Lys(N^e-tetradecanoyl)-OH (SEQ ID NO: 8).--

Please replace the paragraph at page 11, lines 15-22 with the following:

--Fmoc-Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr-Lys-OH (SEQ ID NO: 8) (obtained from Bachem Feinchemikalien AG, Switzerland) which is a potent inhibitor of renin was allowed to react with tetradecanoic acid succinimidyl-N-hydroxy ester as described in Example 1. After the acylation reaction, the Fmoc group was removed by addition of piperidine to the reaction mixture to a final concentration of 20%. The title compound was isolated by RP-HPLC as described in Example 1. The yield was 23 mg.--

Please replace the paragraph at page 11, lines 29-36 with the following:

-Reference

The reference compound, H-Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr-Lys-OH (SEQ ID NO: 8), was synthesized from Fmoc-Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr-Lys-OH (SEQ ID NO: 8) (obtained from Bachem Feinchemikalien AG, Switzerland). Thus, 20 mg of Fmoc-Pro-His-Pro-

Phe-His-Phe-Phe-Val-Tyr-Lys-OH (SEQ ID NO: 8) was dissolved in 500 μ l of 20% piperidine in DMF and left for 20 min. The reference compound was purified by RP-HPLC as described in Example 1.--

Please replace the paragraph at page 14, lines 6-15 with the following:

--Human (H-Ser-Leu-Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr-Lys(N^c-tetradecanoyl)-COOH) (SEQ ID NO: 9) was synthesized by standard Fmoc solid phase peptide synthesis (Methods in Molecular Biology, Vol 35: Peptide Synthesis Protocols). The ϵ -amino group of the C-terminal lysine was acylated using tetradecanoic acid succinimidyl-N-hydroxy ester according to the procedure described below. The synthesis was performed manually in polypropylene syringes, on a resin based on a low cross linked polystyrene backbone grafted with polyoxyethylene (TentaGel Resin).--